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AdvaMed
Advanced Medical Technology Association

Friday, August 20, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0194
Definition of Primary Mode of Action of a Combination Product

Dear Sir or Madam:

AdvaMed respectfully submits these comments to the Food and Drug Administration ("FDA") in response to a May 7, 2004 notice requesting comments on the Agency's proposal to amend its combination product regulations to define "mode of action" and "primary mode of action."[1/]

AdvaMed, the Advanced Medical Technology Association, represents more than 1,200 innovators and manufacturers of medical devices, diagnostic products and medical information systems. Its members produce nearly 90 percent of the $75 billion in health technology products consumed yearly in the United States and nearly 50 percent of the $175 billion purchased around the world annually. AdvaMed members range from the largest to the smallest medical technology innovators and companies. Nearly 70 percent of our members have fewer than $30 million in sales annually. A significant and growing percentage of our member companies have health care products that incorporate combination technology, the subject of FDA's request for comments.

AdvaMed applauds the FDA's efforts to improve the transparency, predictability, and consistency of the Agency's jurisdictional assignment of combination products. Since 1991, when FDA's product jurisdiction regulations were promulgated, there have been exponential advances in technology—advances that have led to an increased number of complex,

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1/ 69 Fed. Reg. 25527 (May 7, 2004). In June, the FDA extended the comment period for this proposal to August 20, 2004. 69 Fed. Reg. 35277 (June 24, 2004).

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innovative combination products requiring jurisdictional designation. FDA's efforts to standardize and clarify the designation process will facilitate the review and approval of these innovative products that have the potential to so significantly improve our public health.

The FDA has proposed a primary mode of action assignment that combines a new definition of "primary mode of action," with a supplemental two-tiered assessment to be used when the primary mode of action cannot be determined with "reasonable certainty." More specifically:

- Under the proposal, the Agency will first consider the primary mode of action—that is, the mode of action which represents "the most important therapeutic action of the combination product" (i.e., drug, device, or biological product).[2/]

- If the Agency is unable to determine the primary mode of action "with reasonable certainty," the Agency proposes, as a next-tier assessment, to consider assignment to the "agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole."[3/]

- If jurisdiction is still unable to be determined because there have been no similar precedents, as a second-tier assessment, the Agency proposes to assign the combination product to the "agency component with the most expertise related to the most significant safety and effectiveness questions presented by the combination product."[4/]

AdvaMed's comments, with respect to this algorithm and the proposed rule generally, are provided below.

I. The Role of Precedents

A significant concern of AdvaMed and its members is that, as the proposal is written, precedents do not appear to be considered in the initial determination of primary mode of action. It is understood, however, that this apparent omission at the first stage of the Agency's analysis, is not intentional. More specifically, in meetings and discussions with stakeholders, FDA officials have advised that the proposed rule is not intended to depart from precedents developed over the years, reflected in the intercenter agreements, through requests for designation and product review and clearance/approval processes. The preamble to the proposal also indirectly reflects this intention, stating that the proposed rule "would merely clarify and codify principles the agency has generally used since section 503(g) of the

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2/ 69 Fed. Reg. at 25532 (proposed Section 3.2(m)).

3/ Id. (proposed Section 3.4(b)).

4/ Id.

act was issued in 1990."[5/] Notwithstanding these references, as currently drafted, the proposed rule only appears to consider precedents at the first tier of the two-tiered assignment algorithm—that is, only if the primary mode of action cannot be determined with reasonable certainty.

Given the potential jurisdictional concern and confusion that could arise—particularly with companies that have relied on prior jurisdictional decisions over the years to build their product franchises and businesses—AdvaMed proposes that the proposal clarify the important role of precedents. More specifically, AdvaMed requests: (1) that FDA expressly state in both the preamble and the regulation, that jurisdictional precedents will inform and guide FDA's decision as part of the initial assessment of primary mode of action; and (2) that the preamble emphasize FDA's intention not to change decisions previously made through requests for designation and product review processes. AdvaMed's proposed revision to existing 21 C.F.R. § 3.4(a) and suggested preambular language to accompany this proposed revision, is as follows:[6/]

> 21 C.F.R. § 3.4
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> "(a) To designate the agency component with primary jurisdiction for the premarket review and regulation of a combination product, the agency shall determine the primary mode of action. Prior jurisdictional decisions, made through agreements, requests for designation or product review processes, shall inform and guide FDA's decision. Where the primary mode of action ..."
>
> Preamble
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> "The Agency has revised section 3.4(a) to add new language, clarifying that jurisdictional precedents will be considered by the FDA in its initial determination of primary mode of action, and not only at the first tier of the assignment algorithm. Jurisdictional precedents shall include decisions made through agreements, the request for designation ("RFD") process and product review processes. Additionally, the Agency confirms that the final rule is not intended to change prior jurisdictional decisions made through the product review process or other mechanisms outside the RFD process."

5/ Id. at 25528.

6/ The proposed new language is underlined.

II. The Status of the Intercenter Agreements

AdvaMed also requests preambular confirmation that the Intercenter Agreements will remain in force, as has been conveyed by Agency officials in stakeholder meetings. Acknowledgement of the Intercenter Agreements' continuing force is consistent with the requirements of Section 204 of the Medical Device User Fee and Modernization Act ("MDUFMA"), which calls upon the Agency to "consult with stakeholders" on the issue of whether "to continue in effect, modify, revise, or eliminate [A]greement[s]" specific to the assignment of combination products.[7/] Since this formal consultative review of Agreements has not occurred, and, more importantly, since the Agreements continue to provide significant interpretive guidance to both FDA and industry on the issue of primary mode of action, we request that these documents remain in effect. Examples of their continuing value include the following:

(1) First and foremost, the Agreements provide numerous useful examples of various types of combination products, and the lead Center and regulatory pathway that the FDA would assign to such products. A principal theme for many of these examples,[8/] is that products that have primarily a structural, physical, repair, or reconstruction purpose, are to be regulated as devices. From this general theme, the FDA has determined over the years that the following combination products, among many others, should be regulated as devices: porcine-derived protein matrices for periodontal use; bone cements containing antimicrobial agents; human fibroblast-derived skin substitutes; dental devices with fluoride; condoms, diaphragms, or cervical caps with contraceptive or antimicrobial (including virucidal) agents; cardiac pacemaker leads with steroid-coated tips; surgical or barrier drapes coated or impregnated with antimicrobial drugs; urinary and vascular catheters coated/impregnated with antimicrobial agents; and spinal fusion products containing biomaterials.

(2) The Agreements also provide clarifying guidance concerning factors that determine whether a product is a single entity or a combination product (the latter of which would trigger a primary mode of action analysis). This Intercenter Agreement language is important particularly for infusion pumps and other drug delivery devices, which can be either single entity or combination products, depending on how they are configured, marketed, and labeled. Specifically, the Intercenter Agreement between the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) clarifies that infusion pumps and other drug delivery devices that are distributed unfilled and do not require a change in drug labeling, are

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7/ Section 204 of the Medical Device User Fee and Modernization Act, codified at Section 503(g)(4)(F) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 503(g)(4)(F).

8/ Intercenter Agreement between the Center for Drug Evaluation and Research ("CDER") and the Center for Devices and Radiological Health ("CDRH") (Oct. 31, 1991) (hereinafter referred to as the "CDER/CDRH Intercenter Agreement").

devices regulated by CDRH.[9/] Without this important language, clarifying that these products are devices and not combinations, there is a risk that the proposed primary mode of action analysis would be applied inappropriately, with unintended consequences. Specifically, as the algorithm is currently constructed, jurisdiction would redirect regulation of the majority of unfilled delivery systems to CDER or CBER (Center for Biologics Evaluation and Research), rather than to CDRH, where they historically have been reviewed.

(3) As further clarifying guidance concerning circumstances where device jurisdiction is warranted, the Intercenter Agreement between CDER and CDRH states that:

> For a drug delivery device and drug that are developed for marketing to be used together as a system, a lead center will be designated .... If a drug has been developed and marketed and the development and studying of device technology predominates, the princip[al] mode of action will be deemed to be that of the device, and CDRH would have the lead. If a device has been developed and marketed and the development and studying of drug predominates, then, correspondingly, CDER would have the lead.[10/]

This language historically has protected the ability of delivery systems to be regulated as devices by CDRH in a wide variety of circumstances, (e.g., where drugs are older and off-patent and the device technology issues predominate). These Intercenter references should be preserved, not simply because they reflect Agency precedents, but because they help to promote FDA's initiative to encourage development and efficient premarket review of novel delivery systems.[11/]

(4) As another important point of guidance, the Intercenter Agreement between CDER and CDRH includes a section for determining the primary mode of action of implants, including injectable materials. Specifically, the guidance states that implants and injectable material "placed in the body for primarily a structural purpose even though such a[n] implant may be absorbed or metabolized by the body after it has achieved its primary purpose will be regulated as a device by CDRH." This guidance has been important to a number of products in the wound management, orthopedic, dental, osteoarthritis, and dermal aesthetic sectors, and should be retained as jurisdictional guidance for affected industries. Similarly, the Intercenter Agreement between the

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9/ CDER/CDRH Intercenter Agreement, at VII.A.1(a). See also 21 C.F.R. § 3.2(e)(3). In assessing whether drug labeling would require changes, the CDER/CDRH Intercenter Agreement also provides general guidance on when more minor changes to drug-device instructions for use, can be made through device labeling. See CDER/CDRH Intercenter Agreement, at VII.A.1(a).

10/ CDER/CDRH Intercenter Agreement, at VII.A.1(a).

11/ FDA News, FDA Launches Initiative to Improve the Development and Availability of Innovative Medical Products (Jan. 31, 2003).

> Center for Biologics Evaluation and Research ("CBER") and CDRH states that "[c]ultered skin will be regulated by CDRH under the Medical Device Authorities." This language, like the injectable implant language of the CDER-CDRH Intercenter Agreement, has helped to establish the jurisdictional framework for a number of wound management and skin replacement products, and should be retained to ensure continued CDRH review of those products.[12/]

Given all of these references that further interpret primary mode of action in important ways, AdvaMed requests specific preambular acknowledgement, such as the following, confirming that the Intercenter Agreements will continue in force and effect: "The Agency confirms that the Intercenter Agreements referenced at 21 C.F.R. § 3.5(a)(1) remain in force and effect, even after issuance of this final rule on primary mode of action."

III. Primary Mode of Action

As noted, the first decision point in FDA's proposed algorithm is to determine the "primary mode of action" of the combination product, defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combined product."[13/] The

proposed regulation then further defines "the most important therapeutic action" as "the mode of action expected to make the greatest contribution to the overall therapeutic effects of the combination product."[14/] AdvaMed's comments on this aspect of the proposal follow.

A. Primary Mode of Action Definition

FDA's proposed rule defines "mode of action" and "primary mode of action" with the term "therapeutic action." Because the term "therapeutic action" is more commonly used in connection with drugs and biologics, AdvaMed believes that use of this term could result in too narrow a consideration of primary mode of action. Focusing only on the therapeutic action of a product could undervalue the contribution and function of technology to a combination product, and indirectly cause jurisdictional decisions to be skewed away from devices. To ensure that both technological and clinical aspects of a combination product are given appropriate consideration, AdvaMed requests that the proposal be revised to substitute the word "function" for "action" in the definitions of "mode of action" and "primary mode of action."

Also relating to this standard, AdvaMed agrees with the Agency that primary mode of action assessments over the past decade have included consideration of a product's *intended* function, and appreciates preambular acknowledgement that the definition of primary mode

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[12/] Intercenter Agreement between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health (Oct. 1991).

[13/] 69 Fed. Reg. at 25532 (proposed Section 3.4(m)).

[14/] Id.

of action should be structured to include this concept. AdvaMed requests, however, that the regulation reflect more directly that intended use of the product as a whole will be considered as part of first-level primary mode of action decisions.

Building off these recommendations, AdvaMed proposes that Section 3.2(k) and 3.2(m) be revised as follows:

> (k) *Mode of action* is the means by which a product achieves the intended therapeutic function or effect. For purposes of this definition, "therapeutic" function or effect should be examined with respect to the combination as a whole."[15/]
>
> (m) *Primary mode of action* is the single mode of action of a combination product that provides the most important therapeutic function or effect...

B. "Device Mode of Action" Definition

The proposed rule has the potential to narrow the scope of both combination products and single entity products that are classified as devices. The proposal's definition of "device mode of action," while generally modeled after the statutory definition of "device," differs from the statute in that it excludes products that have a biological product mode of action. Specifically, under the proposed rule, a constituent part has a "device mode of action" if it meets the definition of "device" set forth at section 201(h)(1) to (3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and does not have a "biological mode of action."[16/] Consequently, not only will this proposed definition cause certain cellular- and tissue-based combination products to be regulated as biological products (notwithstanding their structural, restorative, repair function), it could impact single entity classification decisions of bone and tissue-based products now regulated as devices (e.g., demineralized bone).

Accordingly, AdvaMed proposes that the definition of "device mode of action" be confined to the statutory definition of "device." Use of new definitional language outside the scope of the statute, could have unintended, adverse consequences.

C. Review of Devices by Other FDA Centers

AdvaMed believes that the flowchart accompanying the proposed rule gives undue flexibility to review of combinations with a device primary mode of action, by Centers other than CDRH. In particular, the flowchart states that products with a "device" mode of action will

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[15/] Id. (proposed Section 3.2(k)).

[16/] 69 Fed. Reg. at 25532 (proposed Section 3.2(k)(2)). A constituent part has a biological mode of action "if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings." Id. (proposed Section 3.2(k)(1)).

be assigned to the "agency component with responsibility for that type of device" (emphasis added). This flowchart language may lead some to believe that Centers other than CDRH could assume premarket review authority for particular types of devices. As AdvaMed conveyed in its January 24, 2003 comments, the combination product laws are very clear on premarket authority. In contrast to single-entity products, the statute instructs that, if the primary mode of action is that of a device, "the agency center charged with premarket review of devices [i.e., CDRH] shall have primary jurisdiction."[17] In AdvaMed's view, this provision requires CDRH premarket review assignment in all cases when a combination product's primary mode of action is determined to be a device. Consequently, as further supported by its January 2003 comments, AdvaMed requests that the flowchart be revised consistent with the statute (i.e., to state "agency component with responsibility for devices"). Additionally, AdvaMed requests that the Agency include the flowchart in a guidance document. We believe it would be more appropriate for inclusion in a guidance document, consistent with the Agency's practice for other flowcharts and decision trees it has developed.[18]

D. "Reasonable Certainty"

Finally, FDA has stated that it will confine its assignment analysis to a determination of "primary mode of action," unless the product's mode of action cannot be determined with "reasonable certainty." AdvaMed understands from stakeholder discussions that reasonable certainty would turn on the best case for jurisdiction, as offered by both the sponsor and the

Agency. AdvaMed members support the "reasonable certainty" standard, provided that, as noted above, precedents, and intended use of the product as a whole, inform and guide the FDA's judgment of primary mode of action.

IV. Tier One—Agency Component That Regulates Combination Products Presenting Similar Questions of Safety and Effectiveness

AdvaMed members support the next tier of the assignment algorithm, as currently proposed. This tier states that, when it is "not possible to determine with reasonable certainty, which mode of action provides the greater contribution to the overall therapeutic effect of a combination product," FDA will "assign the product to the agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole."[19] AdvaMed members believe that, at this stage of the assignment process, precedents should determine—not simply inform—jurisdictional outcomes.

A failure to consider precedents presents the potential for multiple premarket review regimes for the same core technology. Multiple premarket review regimes trigger a substantial

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[17] Section 503(g)(1)(B) of the FFDCA, 21 U.S.C. § 353(g)(1)(B).

[18] See, e.g., FDA, Deciding When to Submit a 510(k) for a Change to an Existing Device (Jan. 10, 1997).

[19] 69 Fed. Reg. at 25532 (proposed Section 3.4(b)).

investment of additional redundant resources, time and personnel, that could hinder future product development for many companies.

While AdvaMed supports the proposed regulatory language in this first tier of the algorithm, we note that the preamble refers to whether an agency component has "direct experience" with combination products presenting similar questions of safety and effectiveness. We believe that this reference to "direct experience"—language that is not duplicated in the proposed regulation—may inadvertently narrow the consideration of precedents, and therefore, request that the preamble to the final rule clarify that "direct experience" is not part of the analysis.

V. Tier Two—The "Agency Component with the Most Expertise"

When an assignment decision cannot be made at the first tier, the proposed algorithm directs assignment to the agency component with "the most expertise related to the most significant safety and effectiveness questions presented by the combination product." AdvaMed is concerned that the references to the agency component with the "most expertise" will cause divisiveness within the Agency and industry.

We recommend that this second tier focus instead simply on the most significant safety and effectiveness questions presented by the combination product. In considering the most significant safety and effectiveness questions, AdvaMed requests that these judgments be made on a case-by-case basis. The preamble to the proposed rule suggests that the "most significant safety and effectiveness questions" would be determined based on an assessment of a combination product's "relative risks." Risks may not always be the driving factor to determine those issues most significant to the sponsor and FDA. For example, for combinations involving novel technology and an older, off-patent drug with a well-established risk profile, the novel device technological questions may represent the most significant issues, and the established risk profile of the drug may be subordinate to the jurisdictional determination. AdvaMed, therefore, requests that references to "relative risks" be deleted from the preamble, to preserve case-by-case flexibility in this tier of analysis.

AdvaMed also believes that the fostering of innovation should be a factor considered under this tier. Over the years, in enacting the device laws, Congress has repeatedly emphasized the importance of promoting innovation and "least burdensome" requirements, while ensuring safety and effectiveness.[20/] As a result, devices have benefited from regulatory mechanisms available only to products regulated under device authorities.[21/] Further, in recent years, the FDA has launched important new initiatives intended to further promote

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[20/] For example, the legislative history of the Safe Medical Devices Act confirmed that, one of the primary goals of the 1972 Amendments was "to avoid overregulation, thus eliminating unnecessary resource costs to industry and the government, foster incentives to encourage innovation in a relatively youthful industry and, most importantly, provide the public reasonable assurance of safe and effective devices." S. Rep. No. 101-513, at 13 (1990); 130 Cong. Rec. S17457 (daily ed. Oct. 27, 1990).

[21/] These include: early collaboration meetings; 100-day meetings; modular reviews; third party reviews; real time reviews; and humanitarian device exemptions.

medical product innovation. The "Improving Innovation in Medical Technology" and "Critical Path to New Medical Products" initiatives,[22/] are specifically intended to advance innovation of new medical technologies, by, among other things, facilitating Agency use of a variety of premarket resources and tools. Consistent with these initiatives, the FDA can avail itself of whatever expertise is needed for particular issues, through consultation, collaboration, outside experts, and related mechanisms.[23/] Otherwise stated, issue management should not be driven so rigorously by Center designation, if, in so doing, it may stifle innovation. AdvaMed thus requests that innovation themes be identified in preambular discussion, and considered alongside issue management concerns, at this second tier of the algorithm.

VI. Examples

AdvaMed is concerned generally that the examples provided in the proposed rule are few in number, lack complexity, and are not forward-looking. Although we understand that FDA officials have spent considerable time and effort testing the proposed algorithm against a number of actual and hypothetical examples, the Agency has shared only three examples with the public: conventional drug-eluting stents; drug-eluting disc; and a contact lens combined with drug to treat glaucoma. Industry believes that additional examples are essential to a clear understanding of how the algorithm will be applied, and, until such understanding is obtained, it is difficult to provide meaningful comments on the proposed algorithm. Further, inclusion of more examples will better ensure that the rule will be consistently and fairly interpreted, by helping to establish the framework for jurisdictional decisions.

AdvaMed also notes that the examples provided lack complexity, and may inadvertently support the perception that devices generally present less complex issues. For example, even old categories of products, such as contact lenses, evolve through novel technology, and, thus, it cannot be presumed that a contact lens component will present only "routine issues." Further, the designation decision may differ, depending on: (1) whether the drug component is an old, generic, off-patent drug; (2) if the mode of administration and dosage of drug are changed only slightly from that approved; (3) if the drug indication remains the same; or (4) if only secondary aspects of drug labeling (e.g., precautions) change. AdvaMed, therefore, requests that at least one of the examples provided in the preamble include these types of variables to demonstrate how such factors could affect the assignment outcome.

[22/] FDA News, FDA Launches Initiative to Improve the Development and Availability of Innovative Medical Products (Jan. 31, 2003); FDA News, Advancing America's Health, Advancing Medical Breakthroughs. "Critical Path" Paper Calls for Academic Researchers, Product Developers, and Patient Groups to Work with FDA to Help Identify Opportunities to Modernize Tools for Speeding Approvable, Innovative Products to Improve Public Health (Mar. 16, 2004).

[23/] Section 503(g) of the FFDCA, 21 U.S.C. § 353(g) ("Nothing in this subsection shall prevent the Secretary from using any agency resources of the [FDA] necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article"); 21 C.F.R. § 3.4(b).

Finally, the examples provided are based on existing technology and, thus, are not sufficiently forward-looking. If the examples do not anticipate future product innovations, AdvaMed is concerned that, over time, outdated and unhelpful guidance will be locked into law.

To facilitate the Agency's consideration of examples that are more forward-thinking and complex, and not previously provided in the Intercenter Agreements, we have provided at Attachment 1 several combination product examples that would benefit from FDA commentary. Because technology will continue to evolve at a rapid pace, AdvaMed recommends that examples such as those provided at the Attachment be included in a formal guidance document (with FDA's jurisdictional decision for each example and the rationale for each decision), so that the examples can be updated as technology improves, rather than be locked into law.[24/] Additionally, we request that all significant precedent decisions not covered by the Intercenter Agreements be included in such guidance document, or, alternatively, posted on the FDA's website.

Given the importance of these examples to industry's understanding of the proposed rule's application, AdvaMed requests that guidance be issued for comment, prior to finalization of the primary mode of action rule. Finally, because examples provided in guidance or by some other mechanism, will clarify for industry how the proposed rule will be applied, we respectfully request that the Agency issue another proposal before issuing the document as a final rule.

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In conclusion, AdvaMed commends the Agency for its efforts to simplify the designation framework, and improve the transparency, predictability and consistency of the designation process. We appreciate the opportunity to comment on the Agency's proposal, look forward to further interactions with the Agency on these important issues, and welcome a draft guidance document and reproposed rule that responds to comments our members have identified.

Sincerely,

Carolyn D. Jones

Carolyn D. Jones
Associate Vice President
Technology & Regulatory Affairs

[24/] FDA's "Least Burdensome" guidance, which includes hyperlinks to examples and more detailed explanations, may be a useful format to follow. See FDA, The Least Burdensome Provisions of the FDA Modernization Act of 1977: Concept and Principles (Oct. 4, 2002).